A Prospective Study of Whole-Grain Intake and Risk of Type 2 Diabetes Mellitus in US Women

ABSTRACT

Objectives. This study examined the association between intake of whole vs refined grain and the risk of type 2 diabetes mellitus.

Methods. We used a food frequency questionnaire for repeated dietary assessments to prospectively evaluate the relation between whole-grain intake and the risk of diabetes mellitus in a cohort of 75 521 women aged 38 to 63 years without a previous diagnosis of diabetes or cardiovascular disease in 1984.

Results. During the 10-year follow-up, we confirmed 1879 incident cases of diabetes mellitus. When the highest and the lowest quintiles of intake were compared, the age and energy-adjusted relative risks were 0.62 (95% confidence interval [CI] = 0.53, 0.71, *P* trend < .0001) for whole grain, 1.31 (95% CI = 1.12, 1.53, *P* trend = .0003) for refined grain, and 1.57 (95% CI = 1.36, 1.82, *P* trend < .0001) for the ratio of refined- to whole-grain intake. These findings remained significant in multivariate analyses. The findings were most evident for women with a body mass index greater than 25 and were not entirely explained by dietary fiber, magnesium, and vitamin E.

Conclusions. These findings suggest that substituting whole- for refined-grain products may decrease the risk of diabetes mellitus. (*Am J Public Health.* 2000;90:1409–1415)

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In the United States, type 2 diabetes mellitus affects more than 16 million individuals, and approximately 625 000 new cases are diagnosed each year.[1] Despite the public health importance, the optimal diet for the prevention and control of this disease is uncertain.[2]

Until recently, few studies have directly examined the relation of diet to incidence of type 2 diabetes mellitus. High-fat, low-fiber diets have been suggested to increase the risk of insulin resistance and thus lead to the development of type 2 diabetes mellitus. Such a hypothesis is mainly supported by animal experiments[3] showing a reduction in insulin sensitivity associated with high-fat diets[4] and ecologic studies indicating higher incidences of type 2 diabetes mellitus among populations with high consumption of fats.[5]

In a recent review of 9 prospective cohort studies,[6] however, neither total fat nor total carbohydrate intake was related to the risk of type 2 diabetes in men[7,8] or women,[9,10] after adjustment for total energy intake. Moreover, most studies have examined the effects of nutrients and major energy sources isolated from their food sources. Because of the chemical and physical complexity of foods, the effects of individual nutrients eaten as whole foods may not always be the same. Thus, food-based analysis is an important complement to the nutrient-based analysis. Confirmation of a food–disease relation may help elucidate the mechanisms for diet–disease relations and provide a scientific rationale for formulating dietary guidelines.

Compared with refined-grain products, whole-grain products are generally digested and absorbed slowly because of their physical form and high content of viscous fiber, and they elicit smaller postprandial glucose responses, thus exerting less insulin demand on the pancreatic β-cells.[11] In the milling process, the outer bran layer of whole grains is removed and the original physical form is disrupted to make the remaining starchy endosperm more easily digestible. Compared with whole-grain products, refined grains more than double the glycemic and insulinemic responses.[12,13] In addition, various individual antioxidants, nutrients, and phytochemicals in whole grains, as well as interactions among them, are potentially important in modifying the risk of type 2 diabetes mellitus.[14,15]

Despite increasing interest in the potentially beneficial effects of whole-grain foods, epidemiologic data that directly examine whole- vs refined-grain intake in relation to disease risk are sparse.[16,17] To test the hypothesis that high intake of whole grains is associated with reduced risk of type 2 diabetes mellitus, and that high intake of refined grains is related to increased risk, we analyzed prospective data from the Nurses' Health Study from 1984 to 1994 and used multiple assessments of total, whole-, and refined-grain intakes.

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Methods

The Nurses' Health Study is a prospective investigation of diet and lifestyle factors in relation to chronic diseases among 121 700 female registered nurses aged 30 to 55 years at enrollment. The cohort was initiated in 1976, when the participants returned a mailed questionnaire about various dietary and lifestyle risk factors for chronic diseases.[18] In 1980, we assessed diet with a 61-item semiquantitative food frequency questionnaire.[18] In 1984, the food frequency questionnaire was expanded to include 126 items. Because the expanded questionnaires contained numerous additional food items that are important for assessing details of carbohydrate intake, we considered 1984 as the baseline for the current analysis. We excluded respondents with previously diagnosed diabetes, angina, myocardial infarction, stroke, or other cardiovascular diseases in 1984. The final baseline population consisted of 75 521 women aged 38 to 63 in 1984.

Measurements of whole-grain and refined-grain foods, along with other aspects of diet, were repeated in 1986 and 1990 with food frequency questionnaires similar to the questionnaire used in 1984. For each food, a commonly used unit or portion size (e.g., 1 slice of bread) was specified, and the subject was asked how often, on average, during the previous year she had consumed that amount. Nine responses were possible, ranging from "never" to "6 or more times per day." Type and brand of breakfast cereal also were assessed.

The method used to classify whole and refined grains has been described in detail previously.[19,20] Specifically, whole-grain foods included dark bread, whole-grain breakfast cereal, popcorn, cooked oatmeal, wheat germ, brown rice, bran, and other grains (e.g., bulgur, kasha, couscous). Refined-grain foods included sweet rolls and cakes or desserts, white bread, pasta, English muffins, muffins or biscuits, refined-grain breakfast cereal, white rice, pancakes or waffles, and pizza. The list of breakfast cereals reported in the food frequency questionnaire was evaluated for whole-grain and bran content on the basis of data provided on the package labels or by General Mills Co; breakfast cereals with 25% or greater whole-grain or bran content by weight were classified as whole grain.

A full description of the food frequency questionnaires and data on reproducibility and validity in this cohort have been previously reported.[18,21] The performance of the food frequency questionnaire for assessing the individual grain products has been documented to be high.[22] For example, in comparing data from the food frequency questionnaire with detailed diet records in a sample of the participants, correlation coefficients were 0.75 for cold breakfast cereal, 0.71 for white bread, and 0.77 for dark bread.

The primary end point for this analysis was incident type 2 diabetes mellitus that occurred during the 10-year period between the return of the 1984 questionnaire and June 1, 1994. As previously described,[9] detailed supplementary questionnaires were used to confirm the initially reported diabetes and to ascertain the date of diagnosis, tests done to confirm the diagnosis, presenting symptoms, and medications. On the basis of the responses to the supplementary questionnaires, we excluded incident cases of type 1 diabetes and gestational diabetes. After these exclusions, confirmed type 2 diabetes mellitus required at least 1 of the following reported on the supplementary questionnaire:

1. One or more classic symptoms (excessive thirst, polyuria, weight loss, hunger, pruritus, or coma) plus fasting plasma glucose ≥ 140 mg/dL (7.8 mmol/L) or random plasma glucose ≥ 200 mg/dL (11.1 mmol/L);
2. Two or more elevated plasma glucose levels on different occasions (fasting plasma glucose ≥ 140 mg/dL and/or random plasma glucose ≥ 200 mg/dL and/or plasma glucose ≥ 200 mg/dL at ≥2 hours on oral glucose tolerance testing) in the absence of symptoms;
3. Treatment with hypoglycemic medication (insulin or oral hypoglycemic agent).

These criteria correspond to those proposed by the National Diabetes Data Group.[23] The validity of self-reported type 2 diabetes in this cohort with this algorithm was confirmed by medical record review in 61 of 62 women (98%).[24]

In 1997, the diagnostic value for fasting plasma glucose was changed to a lower threshold (≥126 mg/dL, or 7.0 mmol/L) according to the American Diabetes Association's recommendation.[25] For the current analyses, we used the previous guidelines because the Nurses' Health Study was designed and conducted at a time when the National Diabetes Data Group guidelines were still the gold standard. Also, use of a stricter definition of type 2 diabetes can ensure higher specificity of diagnosis and minimize false-positive results, thus minimizing the attenuation of associations between dietary factors and type 2 diabetes.[26]

Person-time for each participant was calculated from the date of return of the 1984 questionnaire to the date of confirmation of type 2 diabetes, death, or June 1, 1994, whichever came first. First, we examined distributions of individual foods to create categories of consumption with adequate person-times at risk in each category. Second, we calculated incidence rates by dividing the number of events by person-time in each category. Third, we estimated relative risks (RRs) as the rate of type 2 diabetes mellitus in a specific category of intake of whole grain, refined grain, or total grain divided by the rate in the lowest category. Fourth, we used multivariate models to adjust for age, smoking, body mass index (BMI), and other probable risk factors. Fifth, we conducted tests of linear trend across increasing categories of grain consumption by assigning the medians of intakes in categories (servings per day) treated as a continuous variable. All P values were 2-sided.

To reduce within-person variation and best represent long-term diet, we used a cumulative average method that employed repeated measures of diet during follow-up. Details of this method have been reported elsewhere.[27] Briefly, we used pooled logistic regression[28] to model the incidence of type 2 diabetes in relation to the cumulative average diet from all cycles of semiquantitative food frequency questionnaires up to the beginning of each 2-year follow-up interval. For example, incidence of type 2 diabetes from 1984 to 1986 was related to dietary intakes assessed on the 1984 questionnaire, incidence from 1986 to 1990 was related to the average intake reported on the 1984 and 1986 questionnaires, and incidence from 1990 to 1994 was related to the average intake from all 3 dietary questionnaires. The basic model included terms for age in 5-year categories, smoking status (never, past, and current classified by number of cigarettes per day), BMI (weight in kilograms divided by height in meters squared, in 6 categories), level of physical activity (hours per week, in 5 categories), family history of diabetes in a first-degree relative (yes or no), alcohol intake (4 categories), use of multivitamins (yes or no), use of vitamin E supplements (yes or no), and total energy intake (in quintiles).

In additional analyses, we included dietary glycemic load in the model to examine whether the effects of whole grains on diabetes mellitus risk persisted when total glycemic load was maintained constant. We also included dietary fiber, magnesium, and vitamin E in the model to examine the extent to which the association between whole-grain intake and diabetes can be explained by these components of whole grain, which are hypothesized to be protective for diabetes.

Results

At baseline in 1984, women with high intake of whole grains smoked less, exercised more, weighed less, and were more likely to use multivitamin or vitamin E supplements than women with low intake of whole grains.

TABLE 1—Age-Adjusted Baseline Characteristics According to Quintiles of Whole-Grain Intake Among 75 521 US Female Nurses Aged 38 to 63 Years in 1984[a]

	Quintile of Whole-Grain Intake				
	1	2	3	4	5
Quintile Median (Range of Servings/Day)	0.13 (0–0.26)	0.43 (0.27–0.56)	0.85 (0.57–1.06)	1.31 (1.07–1.76)	2.70 (1.77–15.93)
Family history of diabetes, %	13	12	12	12	12
Vigorous activity, % (at least once/wk)	36	41	44	47	50
Metabolic equivalent hr/wk[b]	2.85	3.07	3.20	3.36	3.45
Body mass index, kg/m^2	25.0	25.0	25.0	24.8	24.4
Current smoker, %	35	28	23	18	16
Multivitamin use	30	34	37	40	44
Vitamin E supplement use	12	15	17	19	24
Nutrients (daily intake)					
Total energy intake, kcal	1566	1648	1722	1826	1973
Dietary glycemic load	155	156	160	164	170
Carbohydrate, g	178	180	185	190	195
Polyunsaturated fat, g	12	12	12	12	12
Monounsaturated fat, g	24	23	22	22	21
Saturated fat, g	23	23	22	21	20
Trans fatty acids, g	4	4	3	3	3
Cholesterol, mg	292	293	289	281	269
Protein, g	69	70	72	72	73
Dietary fiber, g	14	15	16	18	20
Cereal fiber, g	3	3	4	5	6
Alcohol, g	8	8	7	7	6
Magnesium, mg	248	266	284	304	342
Dietary vitamin E, mg	6	6	6	7	7
Foods (servings/d)					
Dark bread	0.05	0.24	0.44	0.64	1.73
Whole-grain breakfast cereal	0.04	0.14	0.30	0.44	0.55
Brown rice	0.01	0.02	0.03	0.04	0.06
Wheat germ	0.00	0.00	0.01	0.02	0.09
Bran	0.00	0.01	0.02	0.07	0.30
Other grains	0.00	0.00	0.01	0.01	0.02
Cooked oatmeal	0.01	0.03	0.05	0.08	0.11
Popcorn	0.03	0.07	0.10	0.13	0.21

[a]Whole grain includes dark bread, whole-grain breakfast cereal, popcorn, cooked oatmeal, wheat germ, brown rice, bran, and other grains (e.g., bulgur, kasha, couscous). Breakfast cereals with ≥25% whole-grain or bran content by weight were classified as whole grain.
[b]Average time per week spent in vigorous activity.

They also had higher glycemic loads and higher intakes of total calories, carbohydrates, protein, dietary fiber, and cereal fiber but lower intakes of fats, cholesterol, and alcohol (Table 1). Family history of diabetes did not vary appreciably across quintiles of whole-grain intake.

A total of 1879 incident cases of type 2 diabetes mellitus were confirmed among the 75 521 women followed up for 10 years (722 419 person-years). After adjustment for age and total energy intake, no statistically significant association between total grain intake and risk of type 2 diabetes mellitus was observed, whereas whole-grain intake was inversely related to risk, and refined-grain intake was positively related to risk (Table 2).

When the highest and the lowest quintiles of intake were compared, the age and energy-adjusted relative risk of type 2 diabetes mellitus was 0.62 (95% confidence interval [CI]= 0.53, 0.71; $P<.0001$ for trend) for whole grain and 1.31 (95% CI=1.12, 1.53, $P=.0003$ for trend) for refined grain. These associations were attenuated but remained significant after additional adjustment for BMI, cigarette smoking, alcohol intake, history of diabetes in first-degree relative, use of multivitamins, use of vitamin E supplements, physical activity, and total energy intake. When the 2 extreme quintiles were compared, the relative risk was 0.73 for whole grain (95% CI=0.63, 0.89, $P<.0001$ for trend) (Table 2). Among the above covariates, BMI appeared to be the strongest confounding factor: the relative risk of type 2 diabetes mellitus when the 2 extreme quintiles of whole-grain intake were compared decreased to 0.72 (95% CI=0.62, 0.84) after adding BMI into the age- and energy-adjusted model. Adding dietary glycemic load to the multivariate models did not change the observed associations. In particular, the inverse relation between whole-grain intake and risk of type 2 diabetes mellitus remained significant: multivariate-adjusted relative risk was 0.74 (95% CI=0.63, 0.86, $P<.0001$ for trend) when the 2 extreme quintiles were compared.

The risk of type 2 diabetes mellitus associated with whole-grain intake was independent of that associated with refined-grain intake; the relative risks were almost identical whether or not refined grain and whole grain were included in the model simultaneously.

To further evaluate the net effect of refined- vs whole-grain intakes, we created a ratio by dividing refined-grain intake by whole-grain intake and then examined the risk of type 2 diabetes mellitus according to the quintiles of this ratio. Total grain intake was weakly related to the ratio of intake (Spearman r= –0.05), and the correlation between whole- and refined-grain intakes was also weakly related (Spearman r = –0.1). After adjustment for age and total energy intake, the risk of type 2 diabetes mellitus increased across ascending quintiles of the ratio of refined- to whole-grain intake, although this upward trend appeared to plateau after the fourth quintile. Compared with women in the lowest quintile of intake ratio (i.e., those who consumed relatively large amounts of whole grains or small amounts of

TABLE 2—Adjusted Relative Risk of Type 2 Diabetes According to Quintiles of Intake of Grains Among 75 521 US Female Nurses Aged 38 to 63 Years at Baseline, 1984–1994[a]

	Quintile of Consumption					
	1	2	3	4	5	*P* for Trend
Total grain						
Cases	392	356	368	358	405	
Person-years	144 698	144 403	144 438	144 471	144 409	
RR (95% CI)						
Model 1: age, energy-adjusted	1.00	0.86 (0.74, 0.99)	0.83 (0.72, 0.97)	0.77 (0.66, 0.90)	0.84 (0.71, 0.99)	.13
Model 2: multivariate	1.00	0.84 (0.72, 0.97)	0.82 (0.70, 0.96)	0.72 (0.61, 0.85)	0.75 (0.63, 0.89)	.005
Whole grain						
Cases	426	391	407	320	335	
Person-years	141 914	147 351	143 856	145 133	144 164	
RR (95% CI)						
Model 1: age, energy-adjusted	1.00	0.85 (0.74, 0.98)	0.86 (0.75, 0.99)	0.63 (0.55, 0.73)	0.62 (0.53, 0.71)	<.0001
Model 2: multivariate	1.00	0.91 (0.79, 1.05)	0.94 (0.82, 1.08)	0.74 (0.64, 0.86)	0.73 (0.63, 0.85)	<.0001
Refined grain						
Cases	349	369	337	378	446	
Person-years	144 742	144 817	144 095	144 252	144 512	
RR (95% CI)						
Model 1: age, energy-adjusted	1.00	1.08 (0.93, 1.25)	1.01 (0.86, 1.17)	1.12 (0.96, 1.31)	1.31 (1.12, 1.53)	.0003
Model 2: multivariate	1.00	1.09 (0.94, 1.26)	1.01 (0.86, 1.17)	1.09 (0.92, 1.27)	1.11 (0.94, 1.30)	.26
Ratio of refined to whole grain						
Cases	320	344	369	410	436	
Person-years	144 517	144 335	144 400	144 505	144 661	
RR (95% CI)						
Model 1: age, energy-adjusted	1.00	1.13 (0.97, 1.31)	1.26 (1.08, 1.47)	1.46 (1.26, 1.69)	1.57 (1.36, 1.82)	<.0001
Model 2: multivariate	1.00	1.09 (0.93, 1.27)	1.15 (0.99, 1.33)	1.27 (1.09, 1.47)	1.26 (1.08, 1.46)	.01

Note. RR = relative risk; CI = confidence interval.

[a]Multivariate model 2 includes the following: age (5-year categories); body mass index (6 categories); physical activity (hours per week, in 5 categories); cigarette smoking (never, past, and current smoking of 1–14, 15–24, and ≥25 cigarettes per day); alcohol intake (4 categories); family history of diabetes in a first-degree relative (yes or no); use of multivitamins or vitamin E supplements (yes or no); and total energy intake (in quintiles).

refined grains), women in the highest quintile had a 57% greater risk of type 2 diabetes mellitus (Table 2). After further adjustment for known confounding factors, the positive association between ratio of refined- to whole-grain intake and risk of type 2 diabetes mellitus was still evident (RR = 1.26; 95% CI = 1.08, 1.46; $P = .01$ for trend) when the extreme quintiles were compared. Including saturated and trans fats in the models had essentially no effect on the relative risks.

We also examined the potential interaction between the ratio of refined- to whole-grain intake and saturated fat on type 2 diabetes mellitus risk through stratified analysis. We observed basically the same consistent positive association between the ratio of refined to whole grains and the risk of type 2 diabetes mellitus regardless of levels of saturated fat intake (data not shown).

Of the total 1879 cases of type 2 diabetes mellitus, 1475 cases occurred among women with a BMI greater than 25. Because BMI was the major confounding factor, we examined the association between the ratio of refined- to whole-grain intake and the risk of type 2 diabetes mellitus among women with a BMI greater than 25. Similar findings were observed among this subgroup: the multivariate-adjusted relative risks across ascending quintiles were 1.00, 1.07, 1.14, 1.25, and 1.33 (95% CI = 1.12, 1.56 for the highest quintile, $P = .001$ for trend). To address potential biases from subclinical disease, we excluded cases of type 2 diabetes mellitus in the first 4 years of follow-up in a sensitivity analysis. The multivariate-adjusted relative risks were almost identical to those observed in the full cohort (the multivariate-adjusted relative risks across ascending quintiles of refined- to whole-grain ratio were 1.00, 1.09, 1.17, 1.27, and 1.26; $P = .02$ for trend). In addition, the multivariate-adjusted relative risks remained unchanged when analyses were further restricted to these symptomatic cases of type 2 diabetes mellitus (data not shown).

To elucidate these relations further, we examined the individual foods that contributed to whole-grain consumption in relation to the risk of type 2 diabetes mellitus. After adjustment for the same covariates in multivariate model 2 in Table 2, including total energy intake and potential risk factors, statistically significant inverse associations with type 2 diabetes mellitus were observed for most of the individual foods contributing to whole-grain intakes (Table 3).

Discussion

Results from this large prospective study of adult US women provide support for the hypothesis that whole-grain intake is inversely associated with the risk of type 2 diabetes mellitus. A high ratio of refined- to whole-grain intake (i.e., higher intake of refined grains or lower intake of whole grains) was significantly related to increased risk of type 2 diabetes mellitus. These findings were independent of both dietary and nondietary risk factors for type 2 diabetes mellitus.

Because dietary assessments were conducted before type 2 diabetes was diagnosed, recall bias was unlikely to have affected our findings. Type 2 diabetes mellitus was self-reported, raising the issues of misclassification and underdiagnosis. However, such a limitation would be expected to be small in this cohort of nurses compared with the general population, because of the relative homogeneity regarding the access to medical care. For example, more than 98% of the participants in the Nurses' Health Study visited a physician for a physical examination, breast examination, mammogram, sigmoidoscopy, or colonoscopy at least once between 1988 and 1990. In addition, we used a supplementary ques-

TABLE 3—Multivariate-Adjusted Relative Risk (95% Confidence Interval) of Type 2 Diabetes According to Intake of Specific Whole-Grain Foods Among 75 521 US Female Nurses Aged 38 to 63 Years at Baseline, 1984–1994[a]

Whole-Grain Foods	Almost Never	Amount of Consumption (Servings)				*P* for Trend
		<1/wk	2–4/wk	5–6/wk	≥1/d	
Dark bread	1.00	0.90 (0.77, 1.04)	0.87 (0.75, 1.01)	0.79 (0.66, 0.94)	0.77 (0.66, 0.90)	.002
Whole-grain breakfast cereal	1.00	0.81 (0.71, 0.93)	0.70 (0.60, 0.81)	0.71 (0.62, 0.82)	0.66 (0.55, 0.80)	<.0001
Popcorn	1.00	0.89 (0.81, 0.99)	1.00 (0.85, 1.17)	0.84 (0.62, 1.15)	0.88 (0.59, 1.31)	.47
Cooked oatmeal	1.00	0.97 (0.88, 1.07)	0.84 (0.69, 1.03)	0.61 (0.32, 1.15)	0.73 (0.35, 1.54)	.08
Brown rice	1.00	0.77 (0.69, 0.86)	0.64 (0.44, 0.91)	0.47 (0.15, 1.45)	. . .	<.0001
Wheat germ	1.00	0.64 (0.51, 0.80)	0.79 (0.51, 1.22)	0.85 (0.52, 1.37)	. . .	.003
Bran	1.00	0.66 (0.56, 0.78)	0.63 (0.48, 0.83)	0.54 (0.41, 0.72)	. . .	<.0001
Other grains	1.00	0.77 (0.63, 0.94)	. . .	. . .	. . .	.02

Note. Each category was defined as it was originally asked in the questionnaire; categories with too few type 2 diabetes mellitus cases were combined with adjacent categories to obtain stable estimates.

[a]Multivariate model includes the following: age (5-year categories); body mass index (6 categories); physical activity (hours per week, in 5 categories); cigarette smoking (never, past, and current smoking of 1–14, 15–24, and ≥25 cigarettes per day); alcohol intake (4 categories); family history of diabetes in a first-degree relative (yes or no); use of multivitamins or vitamin E supplements (yes or no); and total energy intake (in quintiles).

tionnaire to ensure a high specificity of diagnosis—61 of 62 cases were confirmed with medical records—and thus minimize the possibility of observing a spurious association between whole-grain intake and type 2 diabetes mellitus.[26]

Aside from chance, several alternative explanations should be considered in the interpretation of these findings. First, the association between whole-grain intake and type 2 diabetes may be explained by other healthy-lifestyle factors associated with high whole-grain intake. However, the increased risk associated with a higher ratio of refined- to whole-grain intake persisted in multivariate models that adjusted for known risk factors. In addition, these findings remained robust among women with a BMI greater than 25 and among never smokers and women with no regular vigorous physical activity (data not shown).

Second, some subclinical conditions might lead to changes in diet and may therefore distort the associations between whole-grain intake and risk of diabetes. We could not address these issues directly. However, any biases from these sources were more likely to attenuate the protective effect of whole grains, because the tendency would be for those who perceived themselves to be at elevated risk for type 2 diabetes to increase consumption of whole grains or change to a better lifestyle. Moreover, the inverse relation between whole-grain intake and risk of type 2 diabetes mellitus was evident in each 2-year interval throughout follow-up and persisted in analyses that excluded cases diagnosed in the first 4 years of follow-up and in analyses restricted to symptomatic cases of type 2 diabetes mellitus.

The overall protective effect of whole grains was observed for individual whole-grain foods, including dark bread, whole-grain breakfast cereal, popcorn, oatmeal, brown rice, wheat germ, bran, and other grains (Table 3). This consistent finding suggests that something present in whole grains may be responsible for the observed protective effect, even though the nutrient content of different whole-grain products may vary. These results are also in close agreement with previous findings from both metabolic and epidemiologic studies on the protective role of dietary fiber in reducing the risk of type 2 diabetes.[29–31] Increased dietary fiber may decrease postprandial glucose and insulin responses in both diabetic and nondiabetic patients.[32,33] We have previously reported inverse associations between dietary fiber, especially cereal fiber, and the risk of type 2 diabetes.[30]

Resistance to insulin-mediated glucose transport and metabolism is an early defect in glucose intolerance and type 2 diabetes mellitus.[34,35] Through increased insulin production by the pancreatic β-cells, hyperinsulinemia compensates for the reduced insulin-dependent glucose disposal to maintain glucose homeostasis. However, with increased demand, β-cells eventually become insufficiently responsive to glucose, and clinical diabetes develops.[36,37] Mechanisms for this insulin resistance–pancreatic exhaustion theory are not fully understood,[38,39] but factors that increase plasma glucose and insulin responses may modulate the effects of insulin resistance, which in turn increases the risk of type 2 diabetes mellitus. Therefore, reduced hyperglycemia and insulin demand may explain a protective effect of higher intake of whole-grain foods.[32,40]

Because of their physical form and high content of viscous fiber, whole-grain products tend to be slowly digested and absorbed and thus have relatively low glycemic indices.[41,42] In some metabolic studies of both diabetic and nondiabetic subjects, high intake of low-glycemic-index foods has been associated with lower levels of glycosylated hemoglobin (Hb A_1c) and urinary C-peptide excretion (marker for β-cell insulin production).[32,43] On the other hand, finely ground fiber from milled-flour foods, such as pancakes and white bread, does not have the same physical properties as fiber from whole-grain sources.[44] For example, whole-meal breads made from milled flour have no effect on the level of postprandial blood glucose response in diabetic patients, because they are readily digested and absorbed. In a randomized trial of 6 adults with diabetes, Jenkins and colleagues[11] examined the metabolic effect of breads with different whole-grain contents and reported a significant trend toward lower glycemic response with an increasing proportion of whole cereal grains in test breads. Lower in vitro digestibility of test breads associated with high whole-grain content also was observed.

Another mechanistic hypothesis invoking specific constituents of whole grains is the antioxidant theory.[17] Oxidative stress has been associated with reduced insulin-dependent glucose disposal and diabetic complications.[45] Lower plasma levels of vitamin E were associated with increased risk of type 2 diabetes in 944 men followed up for 4 years in East Finland,[46] and vitamin E supplementation has been independently associated with improved insulin sensitivity in both diabetic and nondiabetic individuals.[14,15]

Because our primary aim in the current study was to determine the total effect of whole grains on the risk of type 2 diabetes, we did not adjust for dietary fiber, magnesium, and vitamin E in our main statistical models. In secondary analyses, even after dietary fiber, magnesium, and vitamin E were taken into account in multivariate models, an inverse association between whole-grain intake and type 2 diabetes mellitus was evident (RR=0.81, 95% CI=0.69, 0.96, P=.01 for trend when the 2 extreme quintiles were compared), indicating that

the effect of whole grain was not explained entirely by content of fiber, magnesium, and vitamin E. Thus, other antioxidants, nutrients, or phytochemicals in whole grains or interactions among them also may play important roles in risk reduction.

Our results on consumption of specific whole-grain foods in relation to the risk of type 2 diabetes suggest that the inverse relation with whole grain was not driven by a single food or eating pattern. Rather, the physical nature of whole-grain products, which is not represented in food composition tables, may be important in affecting the risk of type 2 diabetes. These data further suggest that dietary guidelines should clearly distinguish whole-grain foods from refined-grain products. Although a large portion of energy from our diet comes from grain products, whole-grain foods account for less than 1 serving per day, on average, in an average 2000-kcal adult diet.[47] The consumption of whole-grain foods in place of refined-grain foods would likely have benefits in reducing the risk of type 2 diabetes and other chronic diseases.[6,20,48,49]

In conclusion, in this large population of women, higher intake of whole-grain foods was associated with lower risk of type 2 diabetes, whereas higher intake of refined grain was related to increased risk. The inverse association was independent of known risk factors. These findings support the notion that substituting whole-grain for refined-grain food products may lower the risk of type 2 diabetes. □

Contributors

S. Liu planned the study, analyzed the data, and wrote the first draft of the paper. J.E. Manson, M.J. Stampfer, F.B. Hu, E. Giovannucci, G.A. Colditz, C.H. Hennekens, and W.C. Willett assisted with study design and data collection. All authors contributed to the writing of the paper.

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References

1. Harris MI. Summary. In: National Diabetes Data Group, eds. *Diabetes in America: Diabetes Data Compiled 1995.* Bethesda, Md: National Institutes of Health; 1995:1–32. DHHS publication PHS 95-1468.
2. American Diabetes Association. Nutritional recommendations and principles for individuals with diabetes mellitus. *Diabetes Care*. 1998;21: 532–535.
3. Storlein L, James D, Burleigh K, Chisholm D, Kraegen K. Fat feeding causes widespread in vivo insulin resistance, decreased energy expenditure, and obesity in rats. *Am J Physiol*. 1986;251: E576–E583.
4. Storlien LH, Baur LA, Kriketos AD, et al. Dietary fats and insulin action. *Diabetologia*. 1996; 39:621–631.
5. Rewers M, Hamman R. *Risk Factors for Non-Insulin-Dependent Diabetes.* Washington, DC: National Institutes of Health; 1995. NIH publication 95-1468.
6. Liu S. Insulin resistance, hyperglycemia and risk of major chronic diseases—a dietary perspective. *Proc Nutr Soc Aust*. 1998;22:140–150.
7. Salmeron J, Ascherio A, Rimm EB, et al. Dietary fiber, glycemic load, and risk of NIDDM in men. *Diabetes Care*. 1997;20:545–550.
8. Medalie JH, Papier CM, Goldbourt U, Herman JB. Major factors in the development of diabetes mellitus in 10,000 men. *Arch Intern Med*. 1975; 135:811–817.
9. Colditz G, Manson J, Stampfer M, Rosner B, Willett W, Speizer F. Diet and risk of clinical diabetes in women. *Am J Clin Nutr*. 1992;55: 1018–1023.
10. Lundgren H, Bengtsson C, Blohme G, et al. Dietary habits and incidence of noninsulin-dependent diabetes mellitus in a population study of women in Gothenburg, Sweden. *Am J Clin Nutr*. 1989;49:708–712.
11. Jenkins DJ, Wesson V, Wolever TM, et al. Wholemeal versus wholegrain breads: proportion of whole or cracked grain and the glycaemic response. *BMJ*. 1988;297:958–960.
12. Heaton K, Marcus S, Emmett P, Bolton C. Particle size of wheat, maize, and oat test meals: effects on plasma glucose and insulin responses and on the rate of starch digestion in vitro. *Am J Clin Nutr*. 1988;47:675–682.
13. Brand J, Nicholson P, Thorburn A, Truswell A. Food processing and the glycemic index. *Am J Clin Nutr*. 1985;42:1192–1196.
14. Caballero B. Vitamin E improves the action of insulin. *Nutr Rev*. 1993;51:339–340.
15. Paolisso D, D'Amore A, Ceriello A, Varrichio M, D'Onofrio F. Pharmacologic doses of vitamin E improve insulin action in healthy subjects and non-insulin-dependent diabetic patients. *Am J Clin Nutr*. 1993;57:650–656.
16. Slavin JL. Epidemiological evidence for the impact of whole grains on health. *Crit Rev Food Sci Nutr*. 1994;34(5–6):427–434.
17. Slavin J, Jacobs D, Marquart L. Whole-grain consumption and chronic disease: protective mechanism. *Nutr Cancer*. 1997;27:14–21.
18. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol*. 1985;122:51–65.
19. Jacobs DR Jr, Meyer KA, Kushi LH, Folsom AR. Whole-grain intake may reduce the risk of ischemic heart disease death in postmenopausal women: the Iowa Women's Health Study. *Am J Clin Nutr*. 1998;68:248–257.
20. Liu S, Stampfer M, Hu FB, et al. Whole grain consumption and risk of coronary heart disease: results from the Nurses' Health Study. *Am J Clin Nutr*. 1999;70:412–419.
21. Willett WC. *Nutritional Epidemiology.* 2nd ed. New York, NY: Oxford University Press; 1998.
22. Salvini S, Hunter DJ, Sampson L, et al. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. *Int J Epidemiol*. 1989;18:858–867.
23. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes*. 1979;28: 1039–1057.
24. Manson JE, Rimm EB, Stampfer MJ, et al. A prospective study of physical activity and the incidence of non-insulin-dependent diabetes mellitus in women. *Lancet*. 1991;338:774–778.
25. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 1997; 20:1183–1194.
26. Rothman KJ. *Modern Epidemiology*. Boston, Mass: Little, Brown and Co; 1986.
27. Hu F, Stampfer M, Rimm E, et al. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. *Am J Epidemiol*. 1999;149:531–540.
28. Cupples LA, D'Agostino RB, Anderson K, Kannel WB. Comparison of baseline and repeated measure covariate techniques in the Framingham Heart Study. *Stat Med.* 1988;7:205–222.
29. Anderson JW. Fiber and health: an overview. *Am J Gastroenterol*. 1986;81:892–897.
30. Salmeron J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willett WC. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. *JAMA*. 1997;277: 472–477.
31. Marshall JA, Bessesen DH, Hamman RF. High saturated fat and low starch and fibre are associated with hyperinsulinaemia in a non-diabetic population: the San Luis Valley Diabetes Study. *Diabetologia*. 1997;40:430–438.
32. Jenkins DJ, Jenkins AL, Wolever TM. Low glycemic index: lente carbohydrates and physiological effects of altered food frequency. *Am J Clin Nutr*. 1994;59(3 suppl):706S–709S.
33. Jenkins DJ, Josse RG, Jenkins AL, Wolever TM, Vuksan V. Implications of altering the rate of carbohydrate absorption from the gastrointestinal tract. *Clin Invest Med*. 1995;18: 296–302.
34. Kahn CR. Banting Lecture: Insulin action, diabetogenes, and the cause of type II diabetes. *Diabetes*. 1994;43:1066–1084.
35. Eriksson J, Franssila-Kallunki A, Ekstrand A, et al. Early metabolic defects in persons at increased risk for non-insulin dependent diabetes mellitus. *N Engl J Med*. 1989;321:337–343.
36. Haffner S, Stern M, Mitchell B, Hazuda H, Patterson J. Incidence of type II diabetes in Mexican Americans predicted by fasting insulin and glucose levels, obesity, and body-fat distribution. *Diabetes*. 1990;39:283–288.
37. DeFronzo R, Bonadonna R, Ferrannini E. Pathogenesis of NIDDM. *Diabetes Care*. 1992;15: 318–368.
38. Rossetti L, Giaccari A, DeFronzo R. Glucose toxicity. *Diabetes Care*. 1990;13:610–630.
39. Leahy JL, Bonner-Weir S, Weir GC. Beta-cell dysfunction induced by chronic hyperglycemia:

current ideas on mechanism of impaired glucose-induced insulin secretion. *Diabetes Care*. 1992; 15:442–455.
40. Brand-Miller J, Colagiuri S. The carnivore connection: dietary carbohydrate in the evolution of NIDDM. *Diabetologia*. 1994;37:1280–1286.
41. Jenkins DJ, Ghafari H, Wolever TM, et al. Relationship between rate of digestion of foods and post-prandial glycaemia. *Diabetologia*. 1982;22: 450–455.
42. Jenkins D, Wolever T, Kalmusky J. Low-glycemic index diet in hyperlipidemia: use of traditional starchy foods. *Am J Clin Nutr*. 1987;45: 66–71.
43. Wolever T, Bolognesi C. Prediction of glucose and insulin responses of normal subjects after consuming mixed meals varying in energy, protein, fat, carbohydrate and glycemic index. *Nutrition*. 1992;126:2807–2812.
44. Granfeldt Y, Hagander B, Bjorck I. Metabolic responses to starch in oat and wheat products: on the importance of food structure, incomplete gelatinization or presence of viscous dietary fibre. *Eur J Clin Nutr*. 1995;49:189–199.
45. Oberley LW. Free radicals and diabetes. *Free Radic Biol Med*. 1988;5:113–124.
46. Salonen JT, Nyyssonen K, Tuomainen TP, et al. Increased risk of non-insulin dependent diabetes mellitus at low plasma vitamin E concentrations: a four year follow up study in men. *BMJ*. 1995; 311:1124–1127.
47. Anderson GH. Dietary patterns vs. dietary recommendations: identifying the gaps for complex carbohydrate. *Crit Rev Food Sci Nutr*. 1994; 34(5–6):435–440.
48. Jacobs DR Jr, Slavin J, Marquart L. Whole grain intake and cancer: a review of the literature. *Nutr Cancer*. 1995;24:221–229.
49. Liu S, Willett WC, Stampfer MJ, et al. A prospective study of dietary glycemic load, carbohydrates and risk of coronary heart disease in US women. *Am J Clin Nutr.* 2000;71:1455–1461.